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Better prediction of drug response in diabetic kidney disease

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N-terminal pro-brain natriuretic peptide (NT-proBNP) predicts the cardio-renal response to aliskiren in patients with type 2 diabetes at high renal and cardiovascular risk

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Abstract

Sodium retention and volume overload are main determinants of poor response to RAAS inhibition in patients with diabetes. As volume excess can exist without symptoms, biomarkers are needed to identify a priori which patients are volume overloaded and may experience less benefit from RAAS inhibition. N-terminal pro-brain natriuretic peptide (NT-proBNP) is released in the setting of increased cardiac wall stress and volume overload. We conducted a post-hoc analysis among 5081 patients with type 2 diabetes mellitus participating in the ALTITUDE trial to investigate whether NTproBNP can predict the effects of additional therapy with aliskiren on cardio-renal endpoints. Aliskiren compared to placebo reduced the risk of the primary cardio-renal endpoint events by 20% (95%CI: 16 to 61) and 2% (−42 to 30) in the two lowest NT-proBNP tertiles, and it increased the risk by 25% (−4 to 96) in the highest NT-proBNP tertile (p-value for trend = 0.009). Similar trends were observed for the cardiovascular and ESRD end points. Effects of aliskiren compared to placebo on safety outcomes (hyperkalemia and hospitalization for acute kidney injury) were independent of NT-proBNP. In conclusion, baseline NT-proBNP may be used as a marker to predict the response to aliskiren on cardio-renal outcomes when added to standard therapy with RAAS inhibition.

Introduction

The antihypertensive and anti-albuminuric response to RAAS therapy varies considerably between patients with type 2 diabetes.[1,2] Patients with type 2 diabetes are susceptible to retain sodium and fluid due to disturbed insulin homeostasis.[3] Previous studies showed that sodium retention and subsequent volume overload are main determinants of poor response to RAAS therapy.[4,5] Accordingly, volume restriction by means of co-diuretic treatment or low sodium diet enhances the blood pressure and albuminuria lowering effects of RAAS inhibition.[6] Diuretic treatment is therefore recommended, although not always implemented in clinical practice. As volume excess can exist without symptoms, it is difficult to identify a priori which patients are volume overloaded and will have less beneficial response to RAAS inhibition. Therefore, biomarkers that represent volume status and response to RAAS inhibition are desired.

N-terminal pro-brain natriuretic peptide (NT-proBNP) is secreted from the ventricular myocardium in response to increased myocyte stress and volume overload.[7] This suggests that high levels of NT-proBNP may be a marker of excess volume overload in patients without overt heart failure and may be an indicator of response to RAAS intervention.

To test this hypothesis, we performed a post-hoc analysis of the ALTITUDE trial in which patients with type 2 diabetes with increased cardiovascular or renal risk were randomly assigned to aliskiren or placebo treatment on top of treatment with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB). The aim of this study was to determine whether NT-proBNP predicts the response to aliskiren on cardio-renal endpoints.

Materials and Methods

Patients and Study Design

The ALTITUDE trial was a randomized, double-blind, placebo-controlled trial conducted at 854 centres in 36 countries. The study design and principal findings have been published previously.[8] In short, 8561 patients with type 2 diabetes mellitus at high risk of cardiovascular

and renal events were assigned to either aliskiren 300 mg/day or matched placebo in addition to antihypertensive therapy consisting of an individually titrated optimal recommended dose of ACE inhibitor or ARB, but not both. Randomized patients were followed for a median of 32.9 months for occurrence of cardiovascular and renal events. Inclusion criteria were: persistent macroalbuminuria (urinary albumin : creatinine ratio (UACR) ≥ 200 mg/g), an estimated glomerular filtration rate (eGFR) of ≥ 30 to ≤ 60 ml/min/1.73 m^2 and persistent microalbuminuria (UACR ≥ 20 mg/g to ≤ 200 mg/g), or a history of cardiovascular disease (including heart failure NYHA class I/II) and an eGFR of ≥ 30 and < 60 ml/min/1.73 m^2. All patients signed informed consent before enrolment, and the study was approved by the local institutional review board of each participating centre.

Measurements and Outcomes

At each visit, patients submitted three consecutive first morning void samples. Urinary albumin (mg/l) and creatinine (g/l), and thereby albumin to creatinine ratio, were measured in each first morning void sample by immunoturbidimetry. The geometric mean of UACR was calculated from the three first morning void samples and used for analysis. Serum creatinine concentration was measured by Jaffe reaction (Roche Diagnostics). Blood pressure was measured using an automated validated device, while the patient was in sitting position. The mean of three blood pressure measurements with 1–2 minute intervals was used for analysis. eGFR was calculated with the Modification of Diet in Renal Disease (MDRD) formula.[9] NT-proBNP was measured in plasma at baseline. All laboratory analyses, including first morning void urine analysis, were performed at central laboratories in Europe or the United States.

The primary cardio-renal endpoint was defined as a composite of cardiac arrest with resuscitation, non-fatal myocardial infarction, non-fatal stroke, unplanned hospitalization for heart failure, cardiovascular death, end-stage renal disease (ESRD; defined as the need for chronic dialysis, renal transplantation or a serum creatinine concentration > 530 µmol/l (6.0 mg/dl) sustained for at least 1 month), doubling of serum creatinine, or death attributable to kidney failure defined as the need for renal-replacement therapy with no dialysis or transplantation available or initiated. Safety outcomes included acute kidney injury and hyperkalaemia.

All endpoints were adjudicated by a central endpoint committee using rigorous definitions.

Statistical analysis

The effect of aliskiren compared to placebo on cardio-renal and safety outcomes in tertiles of baseline NT-proBNP as well as for continuous measures of NT-proBNP was estimated from unadjusted Cox proportional hazard regression models. For patients who experienced more than one primary event, survival time to the first renal or cardiovascular event was used in each analysis. Patients who did not have an endpoint of interest during the study were censored at the study cut-off date. Test for trends in treatment effects across NT-proBNP tertiles as categorical and continuous variables were conducted by adding interaction terms (NT-proBNP * treatment assignment) to the relevant Cox models. In an additional analysis, the Cox model was adjusted for age, gender, UACR, eGFR, SBP, diastolic blood pressure (DBP), glycated haemoglobin (HbA1c), body mass index, LDL cholesterol, HDL cholesterol, triglycerides, history of cardiovascular disease (yes/no), haemoglobin, potassium, use of diuretics, smoking status (yes/no), and alcohol consumption (yes/no) to assess whether the interaction between baseline NT-proBNP and treatment assignment persisted after accounting for differences in these parameters across NT-proBNP tertiles. These covariates were chosen in accordance with previous analyses in this population. To further delineate the relationship between baseline levels of NT-proBNP and the cardio-renal endpoints, a subpopulation treatment effect pattern plot (STEPP) was used to explore patterns of treatment effect for varying levels of baseline NT-proBNP. STEPP enables the calculation of drug estimates along a continuous scale with overlapping patient subgroups.[10,11] An Analysis of Covariance (ANCOVA) model was used to assess the treatment effect on albuminuria and blood pressure at month six. Test for trends in treatment effects were assessed by adding an interaction term to the ANCOVA model.

For continuous variables that are not normally distributed, such as NT-proBNP and UACR, a natural log transformation was applied before analysis to fulfil assumptions for regression analyses. Differences in baseline characteristics across NT-proBNP tertiles were tested with ANOVA with Bonferroni adjustments for multiple comparisons for

continuous variables. Chi Square tests were used to test differences in categorical variables.

Two-sided p-values < 0.05 indicated statistical significance. Data were analysed with SAS version 9.3 (SAS Institute, Cary, NC).

Results

Of the 8561 patients enrolled in the ALTITUDE trial, 5081 (59.5%) patients had NT-proBNP measurements available and did not have a history of congestive heart failure at baseline. These were included in the analysis. In comparing the characteristics of the overall ALTITUDE population with those in whom NT-proBNP was measured no relevant differences were observed (Supplement Table 1). The baseline characteristics stratified by tertiles of baseline NT-proBNP are presented in Table 1. Median NT-proBNP levels in increasing tertiles of NT-proBNP were 50, 157, and 534 pg/ml, respectively. Patients in the lower NT-proBNP tertile were younger, had lower SBP, a higher eGFR, were less likely to have a cardiovascular disease history, and less likely to use β-blockers or diuretics (Table 1).

Baseline NT-pro BNP predicts effects of aliskiren

The effect of aliskiren compared to placebo on albuminuria and systolic blood pressure was modified by baseline NT-proBNP level (p for interaction albuminuria 0.004 and p for interaction systolic blood pressure 0.009). Aliskiren compared to placebo showed a significant reduction in UACR and SBP of 22.2% (95%CI −29.0 to −14.8) and 3.2 mmHg (95%CI −5.0 to −1.4) in the lowest NT-proBNP tertile, whereas aliskiren had no effect on these surrogates in the upper NT-proBNP tertile (Supplement Figure 1).

The effects of aliskiren on cardio-renal endpoints were also modified by baseline NT-proBNP level (p for interaction = 0.009). In the upper NT-proBNP tertile, aliskiren compared to placebo increased the risk of the cardio-renal endpoint (hazard ratio (HR) 1.25 [95%CI 1.04–1.51]), whereas the hazard ratios associated with aliskiren treatment in the middle and lower tertile were 0.96 [95%CI 076–1.26] and 0.80 [95%CI 0.58–1.10], respectively (Figure 1). A statistically significant trend

Table 1: Baseline characteristics stratified by tertiles of baseline NT-proBNP. Within each tertile, values were stratified for treatment with aliskiren or placebo.

	Tertile 1		Tertile 2		Tertile 3	
	Placebo	*Aliskiren*	*Placebo*	*Aliskiren*	*Placebo*	*Aliskiren*
Number of patients	856	846	860	828	832	859
NT-proBNP (pg/ml)	50 [2.5, 95]	50 [2.5, 95]	157 [95, 266]	158 [95, 273]	524 [266, 40500]	544 [266, 40500]
Age (years)*	59.7 (9.7)	59.9 (9.4)	64.7 (9.2)	65.1 (9.0)	67.5 (9.1)	67.2 (9.1)
Gender, *n (%)**						
Men	623 (72.8)	610 (72.1)	566 (65.8)	545 (65.8)	574 (69.0)	586 (68.2)
Women	233 (27.2)	236 (27.9)	294 (34.2)	283 (34.2)	258 (31.0)	273 (31.8)
Race, *n (%)**						
Caucasian	364 (43.0)	379 (45.2)	469 (54.2)	436 (52.5)	498 (59.5)	518 (60.0)
Black	31 (3.7)	22 (2.6)	19 (2.2)	16 (1.9)	17 (2.0)	7 (0.8)
Hispanic	409 (48.3)	382 (45.5)	333 (38.5)	327 (39.4)	254 (30.3)	280 (32.4)
Other	42 (4.9)	56 (6.6)	44 (5.1)	52 (6.2)	68 (8.1)	58 (6.7)
Systolic BP (mmHg)*	133.3 (15.2)	133.0 (14.7)	137.8 (16.2)	138.1 (15.2)	141.6 (17.0)	140.9 (17.0)
Diastolic BP (mmHg)*	76.0 (8.8)	76.3 (8.7)	73.8 (9.5)	73.7 (9.2)	73.5 (10.6)	73.3 (10.7)
Body mass index (kg/m²)	29.5 (5.9)	29.6 (5.6)	29.5 (5.7)	29.7 (5.9)	29.2 (5.7)	29.2 (5.8)
Hemoglobin (mg/dl)*	13.7 (1.6)	13.6 (1.6)	13.0 (1.7)	13.1 (1.7)	12.7 (1.8)	12.7 (1.8)
Glycated hemoglobin (%)*	7.8 (1.6)	7.9 (1.6)	7.7 (1.6)	7.7 (1.5)	7.6 (1.5)	7.6 (1.5)
HDL cholesterol (mg/dl)*	45.5 (11.7)	45.4 (12.1)	47.0 (13.6)	46.7 (12.4)	47.1 (13.3)	46.6 (13.4)
LDL cholesterol (mg/dl)*	102.3 (36.4)	100.4 (35.6)	98.0 (38.9)	99.9 (36.7)	96.8 (97.1)	97.7 (38.6)
Triglycerides (mg/dl)*	175 [124, 148]	168 [123, 248]	156 [115, 221]	159 [115, 221]	142 [106, 195]	142 [106, 204]
eGFR (mL/min/1.73 m²)†*	67.8 (28.2)	66.4 (27.0)	56.2 (20.0)	56.1 (20.3)	50.4 (17.3)	52.0 (17.8)
UACR (mg/g)*	352 [149, 841]	337 [132, 766]	290 [62, 1006]	314 [60, 891]	326 [55, 1253]	324 [64, 1277]
History of CV disease *(n,%)**	175 (20.4)	171 (20.2)	301 (35.0)	280 (33.8)	416 (50.0)	405 (47.1)
Diabetic retinopathy *(n,%)*	315 (37.2)	304 (36.2)	314 (36.3)	336 (40.4)	345 (41.2)	342 (39.6)
Concomitant medication *(n,%)*						
Betablockers*	268 (31.3)	263 (31.1)	407 (47.3)	405 (48.9)	504 (60.6)	524 (61.0)
Diuretics*	430 (50.2)	431 (50.9)	512 (59.5)	493 (59.5)	560 (67.3)	556 (64.7)
Insulin*	485 (56.7)	481 (56.9)	500 (58.1)	496 (59.9)	481 (57.8)	516 (60.1)
Sulfonylureas	265 (31.3)	255 (30.4)	276 (31.9)	255 (30.7)	273 (32.6)	267 (30.9)
Biguanides*	426 (50.4)	424 (50.5)	363 (42.0)	362 (41.9)	347 (41.5)	362 (41.9)

Numeric variables are presented as mean (SD) if normally distributed and skewed data were presented as median (IQR). NT-proBNP is presented as median (range). Categorical variables are presented as frequency (%). BP, blood pressure; HDL, high density lipoprotein; LDL, low density lipoprotein; eGFR, estimated glomerular filtration rate; UACR, urine albumin: urine creatinine ratio. * Statistically significant between tertiles of NT-proBNP. † Calculated with the Modification of Diet in Renal Disease study equation (MDRD).

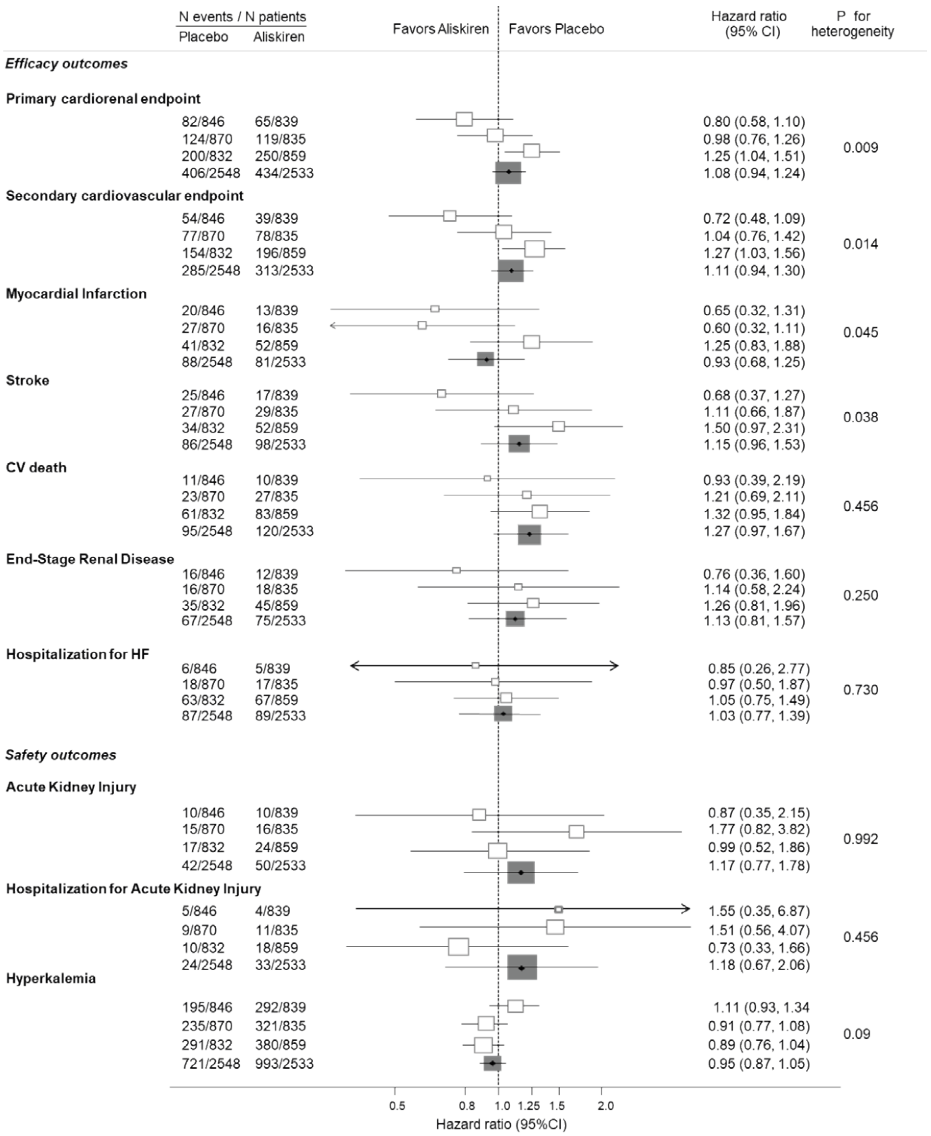

Figure 1. Effect of aliskiren versus placebo on cardiovascular and renal endpoints, and safety outcomes (acute kidney injury, hospitalization for acute kidney injury, and hyperkalemia) according to in tertiles of baseline NT-proBNP.

The solid boxes represent estimates of treatment effects. The center of the boxes are placed on the estimate of the treatment effect, the horizontal line represent the width of the 95% confidence interval. The primary cardio-renal endpoint was defined as a composite of cardiac arrest with resuscitation, non-fatal myocardial infarction, non-fatal stroke, unplanned hospitalization for heart failure, cardiovascular death,

across NT-proBNP tertiles was also observed for the cardiovascular endpoint, myocardial infarction and stroke. A similar trend was observed for ESRD and hospitalization for heart failure, although these trends did not reach statistical significance possibly due to the relatively small number of events. The interaction between aliskiren assignment and NT-proBNP levels persisted ($p = 0.005$ for the composite cardio-renal endpoint) in a multivariable adjusted model. Additionally, there was no difference in interaction between NT-proBNP and aliskiren between patients with and without diuretic use at baseline ($P = 0.48$). The STEPP analyses, in which NT-proBNP was defined as continuous instead of categorical variable, provided results similar to the main analysis and showed that aliskiren tended to increase the risk of cardiorenal events at higher NT-proBNP levels (Supplement Figure 2).

Effect of aliskiren versus placebo on safety outcomes according to baseline NT-proBNP levels

The hazard ratios for adverse event rates in the aliskiren group versus placebo according to the NT-proBNP tertiles are presented in Figure 1. The administration of aliskiren resulted in similar relative effects on hyperkalaemia, acute kidney injury or hospitalization for acute kidney injury irrespective of baseline NT-proBNP levels.

Discussion

This study shows that the relative risks for cardiovascular and renal events achieved with the direct renin inhibitor aliskiren as adjunct to RAAS blockade are modified by baseline NT-proBNP levels. At higher NT-proBNP levels, aliskiren compared to placebo increased the risk of the cardio-renal endpoint, while in the lower NT-proBNP tertile,

end-stage renal disease (ESRD; defined as the need for chronic dialysis, renal transplantation or a serum creatinine concentration > 530 μmol/l (6.0 mg/dl) sustained for at least 1 month), doubling of serum creatinine, or death attributable to kidney failure defined as the need for renal-replacement therapy with no dialysis or transplantation available or initiated. The secondary cardiovascular endpoint was defined as a composite of cardiac arrest with resuscitation, non-fatal myocardial infarction, non-fatal stroke, unplanned hospitalization for heart failure and cardiovascular death.

treatment with aliskiren tended to reduce cardio-renal risk. These results suggest that NT-proBNP, a marker of vascular wall stress and fluid overload, can possibly be used to identify patients more likely to respond to dual RAAS inhibition with aliskiren.

Volume overload is frequently observed in patients with type 2 diabetes at high cardio-renal risk.[12,13] Extracellular volume restriction, by means of moderating dietary sodium intake or concomitant diuretic treatment has been shown to improve the albuminuria and blood pressure lowering response to RAAS blockade as well as the efficacy of RAAS blockade to decrease cardio-renal risk.[5,14,15] This study demonstrates that NT-proBNP can help to identify individuals who may not respond to dual RAAS inhibition with aliskiren and who may benefit from diuretic treatment or dietary sodium lowering. Indeed, it has been shown that hydrochlorothiazide or a low sodium diet is particularly effective in lowering albuminuria and blood pressure in patients with NT-proBNP levels > 125 pg/ml who were already receiving a maximum dose of losartan.[16] Whether diuretic treatment or a low sodium diet as adjunct to RAAS blockade will prevent cardio-renal endpoints in patients with high NT-proBNP requires further study.

The primary results of the ALTITUDE trial showed that aliskiren did not confer renal or cardiovascular protection in high risk patients with type 2 diabetes. We previously showed that patients with a greater than 30% reduction in albuminuria during the first six months of the ALTITUDE trial had a substantially lower cardio-renal risk compared to patients with a modest increase in albuminuria.[17] We now extend these findings and demonstrate that baseline NT-proBNP enables the selection of subgroups of patients who will or will not benefit from aliskiren. We also showed that low and high NT-proBNP levels are independently associated with presence or absence of a reduction in SBP and UACR , while adverse event rates including hyperkalemia and acute kidney injury were similar across NT-proBNP tertiles. Moreover, these results support our previous finding that patients with a lack of reduction in albuminuria are likely volume overloaded and therefore did not respond to aliskiren.

How do the results of our study relate to the current literature? A previous post-hoc analysis of the I-PRESERVE trial in patients with heart failure showed that although NT-proBNP independently predicted all-cause mortality and cardiovascular hospitalizations, the response to

ARB therapy attenuated with higher NT-proBNP levels.[18] Additionally, the efficacy of statins in patients with elevated cardiovascular risk also appears to be higher in patients with lower NT-proBNP levels, although the mechanisms by which statin treatment would be more beneficial in patients with low NT-proBNP are incompletely understood.[19,20] Our study extends these previous findings to a broad population of patients with type 2 diabetes with or without cardiovascular disease and varying levels of kidney function and albuminuria.

The main limitation of this post-hoc analysis of the data from ALTITUDE is that sodium intake and diuretic use were not standardized. Indeed during the trial, patients were advised to start diuretic treatment. However, this limitation may have led to an underestimation of the reported interaction between the aliskiren treatment effects and NT-proBNP levels. Secondly, significant differences in baseline characteristics were observed across NT-proBNP tertiles. It is therefore possible that patients in the highest NT-proBNP tertile were sicker and therefore responded poorly to aliskiren, independent of the actual NT-proBNP level. However, in multivariable Cox regression analyses the interaction between aliskiren treatment and NT-proBNP persisted, suggesting that the interaction was independent of other patient and disease characteristics. Nevertheless, we cannot exclude residual confounding, and a prospectively designed clinical trial is required to prove this hypothesis.

In conclusion, NT-proBNP, a marker reflecting volume overload, may predict the response to aliskiren on surrogate and clinical outcomes when added to conventional therapy with RAAS blockade in patients with type 2 diabetes at high renal or cardiovascular risk.

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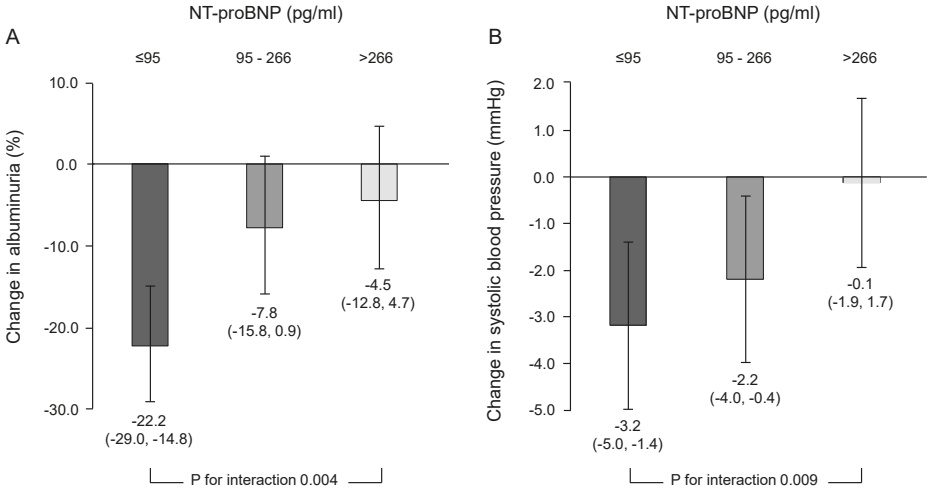
Supplementary files

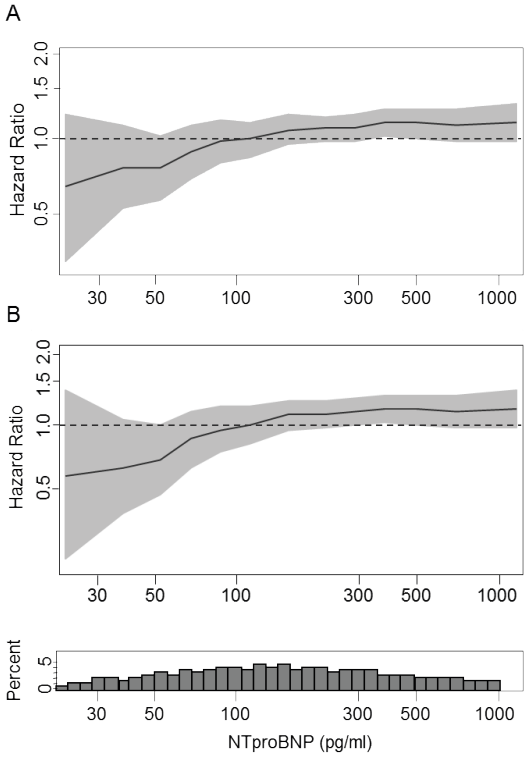
Supplementary **Table 1:** Baseline characteristics in the analyzed population versus those in the total ALTITUDE trial population.

	Analyzed population	Total population
Number of patients	5081	8561
Age (years)	64.0 (9.8)	64.5 (9.8)
Female gender *(n,%)*	1577 (31.0)	2735 (31.9)
Systolic BP (mmHg)	137.5 (16.3)	137.3 (16.5)
Diastolic BP (mmHg)	74.4 (9.7)	74.2 (9.8)
Body mass index (kg/m2)	29.4 (5.8)	29.9 (5.9)
Hemoglobin (mg/dl)	131.3 (17.3)	131.1 (17.2)
Glycated hemoglobin (%)	7.74 (1.55)	7.79 (1.63)
Total cholesterol (mg/dl)	177.4 (47.5)	174.9 (46.6)
LDL cholesterol (mg/dl)	99.3 (37.3)	97.6 (36.7)
eGFR (mL/min/1.73 m²)	58.2 (23.2)	57.0 (22.5)
UACR (mg/g)	36.8 [9.1, 109.2]	32.0 [6.4, 100.5]
History of CV disease *(n,%)*	1748 (34.4)	3619 (42.3)
Concomitant medication *(n,%)*		
Betablockers	2371 (46.7)	4290 (50.1)
Diuretics	2982 (58.7)	5407 (63.2)

Numeric variables are presented as mean (SD) if normally distributed and skewed data were presented as median (IQR). Categorical variables are presented as frequency (%). BP, blood pressure; LDL, low density lipoprotein; eGFR, estimated glomerular filtration rate; UACR, urine albumin: urine creatinine ratio. † Calculated with the Modification of Diet in Renal Disease study equation (MDRD).



Supplementary **Figure 1:** Placebo-adjusted effects of aliskiren on UACR (A) and SBP (B) from baseline to 6 months, in tertiles of baseline NT-proBNP.



Supplementary **Figure 2**: Hazard ratio of the primary cardio-renal endpoint (A) and the secondary cardiovascular endpoint (B) during aliskiren treatment as a function of baseline NT-proBNP, adjusted for placebo.